

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 62-65 are pending in the application, with claim 62 being the independent claim. Claims 1-61 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 62-65 are sought to be added.

Support of claim 62 can be found, for example, in claims 20, 32, and 36 as originally filed. Support of claim 63 can be found, for example, at page 5, paragraph [0063] of the Specification. Support for claim 64 and 65 can be found, for example, in claims 34 and 35 as originally filed.

These changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to Claim 36

The Examiner objected to claim 36 as being in improper form because it is a multiple dependent claim depending from another multiple dependent claim. (*See* Office Action at page 3). Purely in furtherance of prosecution, claim 36 is cancelled. Therefore, this objection has been obviated.

Objection to the Specification

The Examiner objected to the specification as failing to provide proper antecedent basis for claims 21, 24, 26, 27, 29 and 31. (*See* Office Action at page 3). Purely in furtherance of prosecution, and not in acquiescence of any reasoning underlying the Examiner's objection, Applicants have cancelled these claims. Furthermore, none of the new claims sought to be added are directed to the subject matter of these cancelled claims. Therefore, Applicants respectfully request withdrawal of this objection and reconsideration of the specification.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 20, 21, 24, 26, 27, 29, 31, and 33-35 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pluenneke (US 2001/0021380) in view of Fabrizio *et al.* (EP 0 492 448 A1), Horwitz (WO 92/22324), Adair *et al.* (EP 0 516 785 B1), and Reza Dana (WO 00/27421). (*See* Office Action at page 4). The Examiner also rejected claims 20, 31, and 32 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pluenneke in view of Fabrizio *et al.*, Horwitz, Adair *et al.*, and Reza Dana as applied to claims 20, 21, 24, 26, 27, 29, 31, and 33-35, and further in view of Zhu *et al.*, (J. Interferon Cytokine Res. 1999 Jun; 19(6):661-9). (*See* Office Action at page 6). Claims 20, 21, 24, 26, 27, 29, and 31-35 are currently cancelled, thus rendering the rejection of these claims moot. However, because the newly added claims 62-65 encompass the subject matter of cancelled claims 20, 32, 34, and 35, Applicants respectfully submit that claims 62-65 would likewise not have been obvious in light of the references cited by the Examiner, and thus are allowable.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP §2142. The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The Office has recently published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See Examination Guidelines for Determining Obviousness* under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International v. Teleflex Inc. Fed. Reg.* Vol. 72, pp. 57526 to 57535 (October 10, 2007), and MPEP §2143, hereinafter "the Examination Guidelines." Seven rationales are suggested by which obviousness may be found, e.g., by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or substitution were predictable. *Id.*, e.g., at 57529.

Particularly, when a *prima facie* case of obviousness is based on combining prior art reference teachings, the proper analysis is to first consider whether the following three criteria are met: (1) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143.

Applicants respectfully submit that the Examiner has not met the above criteria in alleging the obviousness of claim 62, thus has not established a *prima facie* case of obviousness with respect to claim 62.

Claim 62 encompasses the subject matter of cancelled claims 20, 32, and 36, *i.e.*, the use of F(ab')₂ anti-TNF α fragments in treating corneal transplant rejection.

The Examiner asserts that Pluenneke teaches a method of treating corneal transplant rejection with anti-TNF α antibody by administering the antibody via eyedrops. (*See* Office Action at page 4). However, as the Examiner agrees, Pluenneke does not teach the use of anti-TNF α F(ab')₂ fragments in treating corneal transplant rejection. (*See* Office Action at page 4). Applicants assert that none of the cited prior art references teaches the use of anti-TNF α F(ab')₂ fragments in treating corneal transplant rejection.

Fabrizio discloses an anti-TNF α monoclonal antibody and its ability to neutralize TNF α *in vitro* and *in vivo*. Horwitz discloses a method of producing F(ab')₂ antibody fragments and the potential advantage of better penetration of F(ab')₂ fragments into tumor tissue. Adair discloses a recombinant antibody specific to TNF α and that the antibody can be used in tissue transplant rejection. Reza Dana discloses using TNF α antagonists, such as TNF α receptor, to treat corneal transplant rejection. Zhu discloses that TNF α is hyper-expressed in mouse model of corneal transplant. None of the references cited by the Examiner discloses using F(ab')₂ anti-TNF α fragments in treating corneal transplant rejection.

The Examiner asserts, however:

[I]t has long been known to one of ordinary skill in the art that F(ab')₂ antibody fragments, including F(ab')₂ anti-TNF α fragments in particular, can effectively neutralize their target antigen, such as TNF α , while at the same time being less immunogenic in a human patient than an intact non-

human antibody, easier to grown [*sic*] in microbial cells than an intact antibody, and have better tissue penetration than intact antibodies.

(See Office Action at page 4). Nonetheless, these alleged advantages of using F(ab')₂ antibody fragments were not known to one of ordinary skill in the art to treat corneal transplant rejection. More specifically, none of the cited references discloses the capability of F(ab')₂ anti-TNF α fragments to penetrate the cornea or the level of immunogenicity of F(ab')₂ anti-TNF α fragments in treating corneal transplant rejection.

The cornea is the front part of the eye that covers the iris, pupil, and anterior chamber. The human cornea has five layers including a tough layer, called Bowman's layer, that protects the corneal stroma. (See Basic Histology: Text & Atlas by Luiz Carlos Uchôa Junqueira *et al.* (2005) at page 456). Bowman's layer consists of irregularly-arranged collagen fibers and is seven to twelve microns thick. *Id.* Unlike many other types of tissues, the cornea is transparent and does not have blood vessels. (See Zhu *et al.* at page 1). In light of these special features, Applicants submit that it was not predictable, at the time the instant invention was made, that the F(ab')₂ antibody fragments would better penetrate the cornea even if the fragments might better penetrate a tumor tissue.

Also unlike other types of tissues, the cornea has low constitutive expression of major histocompatibility complex (MHC) antigen, and it does not have centrally situated antigen-presenting cells. *Id.* However, in the cornea, there is local production of immunosuppressive cytokines and expression of Fas ligand. *Id.* These features alter both the induction and expression of alloimmunity. *Id.* Because of these special immune-reaction-related features in the cornea, it was not predictable, at the time of the instant

invention was made, that the lower level of immunogenicity of F(ab')₂ antibody fragments would occur in treating corneal transplant rejection.

Due to the special structural and immune-related features of the cornea, Applicants respectfully assert that the alleged advantages of better tissue penetration and lower level of immunogenicity of F(ab')₂ antibody fragments did not provide an adequate reason to combine the cited reference teachings to arrive at Applicants' claimed invention. At best, the combination of the prior art references are invitation to experiment.

Moreover, the Applicants assert that there was no reasonable expectation that the alleged advantages of using F(ab')₂ antibody fragments in treating a tumor tissue would succeed in treating corneal transplant rejection. The Examiner must not rely on hindsight, for example, using Applicants' own specification as a blue print, to speculate whether there was a reasonable success of using F(ab')₂ antibody fragments to treat corneal transplant rejection. Such a hindsight approach is improper. *See KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1742 (2007) ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.").

Therefore, the Applicants respectfully submit that the Examiner has not met the criteria required to establish a *prima facie* case of obviousness of claim 62 and Applicants respectfully request that the rejection be reconsidered and withdrawn.

Claims 63-65 depend either directly or indirectly on claim 62. Thus, Applicants respectfully submit that claims 63-65 are allowable for at least the same reasons set forth above regarding claim 62, and further in view of their own respective distinguishing

features. *See* MPEP §2143.03, citing *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) ("If an independent claim is nonobvious under 35 U.S.C. § 103, then any dependent claim depending therefore is nonobvious.").


Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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